

Supplemental Data

XLID-Causing Mutations and Associated Genes Challenged in Light of Data From Large-Scale Human Exome Sequencing

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ZNF81 (zinc finger protein 81): **questionable**

An (X;9) *de novo* translocation interrupting *ZNF81* on the X-chromosome and *EHMT1* on chromosome 9 was identified in an intellectually disabled female.¹ Because *ZNF81* is highly homologous to *ZNF41* (considered to be involved in ID) the disruption of *ZNF81* was considered as the cause of ID reported in the individual. In the same study, after screening 300 XLID families including 24 that mapped to the Xp11.2 locus and 217 males with ID, a single nucleotide change c.536G>A (p.Ser179Asn) fully co-segregating with the disease status in the family was detected. Although this missense mutation is not reported in EVS, one truncating variant c.1150A>T (p.Lys384*) is present in one male, while no additional *ZNF81* mutation was detected in the 208 families with suggestive XLID screened by Tarpey *et al.*² Two very recent studies described XLID probands carrying microduplications at locus Xp11.2-p11.3: one encompassing *ZNF81* and two other genes implicated in ID (*FTSJ1* and *SYN1*), the second of 335 kb including *ZNF81* with two genes non associated to cognitive disorders. The authors suggested that *ZNF81* over-expression may thus contribute to the phenotype.^{3, 4} To summarize, the presence of a truncating variant in a male in EVS, while not decisive, weakens the proposed association of *ZNF81* to XLID, that appears excluded for its homolog *ZNF41*.

ATP6AP2 (ATPase H⁺ transporting, lysosomal accessory protein 2, (pro)renin receptor) : **questionable**

The *ATP6AP2*/(pro)renin receptor gene, present in the linkage region of a large family with XLID and epilepsy was sequenced, revealing a silent change c.321C>T (p.Asp107Asp) resulting in splicing aberration in 50% of the transcripts. It was hypothesized that the resulting abnormal protein may have a dominant negative effect.⁵ No other putative mutation was observed in the 25 other genes of the candidate region. The p.Asp107Asp mutation was absent from 1,200 control X-chromosomes and is not reported in EVS. The presence of a splice variant in one male of the NHLBI population is however puzzling and might question the role of *ATP6AP2* in ID and epilepsy. Another *de novo* truncating mutation was recently reported in an abstract form, in an individual with a severe ID/epilepsy phenotype (Chitayat *et al.*, ASHG meeting 2012, G. Nguyen personal communication). Full publication of this observation would lift the ambiguity on *ATP6AP2* involvement in ID.

ZCCHC12/SIZN1 (zinc finger CCHC domain-containing protein 12): **questionable**

Based on its expression in basal forebrain cholinergic neurons, *ZCCHC12/SIZN1* was considered as a good XLID candidate and was screened for mutations in a cohort of 729 ID males.⁶ Two missense mutations were identified: c.1031C>T (p.Thr344Ile) was identified in four affected male sibs in one XLID family and was absent from 494 chromosomes, and c.19C>T (p.Arg7Cys) was detected in four unrelated ID males but was also present in one control individual. This latter variant is present in EVS with a MAF of 0.3% excluding its implication in ID. Since 2008, no additional ID case has been reported with *ZCCHC12* mutations. The implication of *ZCCHC12* in ID thus remains based on the finding of one single missense variant in a single family.

***IGBP1* (immunoglobulin-binding protein 1): never replicated**

IGBP1 encodes the regulatory subunit α -4 of the protein phosphatase 2A (PP2A), which interacts with MID1, the product of the gene mutated in X-linked Opitz GBBB syndrome (MIM#300000) in which clinical manifestations overlap with the ones reported in the FG Syndrome (FGS). In two brothers with suspected FGS and presenting with an agenesis of the corpus callosum, ID and facial dysmorphism, sequence analysis of the FGS1 linked region identified a substitution of two adjacent nucleotides in the 5' UTR of *IGBP1* (c.-57delT and c.-55T>A), marginally affecting its expression (an observed 20% increase).⁷ Both variations were not present in 410 control chromosomes analyzed by Graham *et al.*, and since this region is not covered in EVS we were not able to check for their presence in the larger NHLBI control population. However, other 5' UTR variants located closer to the initiation ATG codon are reported in EVS. This gene, which is present in two XLID diagnostic panel lists, requires additional evidences to strengthen its implication in ID.

***NLGN3* (neuroligin 3): never replicated**

Neuroligins 3 and 4 both encode cell adhesion molecules present at the postsynaptic side of the synapses. Screening of both genes in 36 sib-pairs and 122 trios with ASD led to the simultaneous identification of point mutations in *NLGN4X* and *NLGN3*.⁸ The c.1411C>T; p.Arg451/471Cys missense change identified in *NLGN3* in two brothers with ASD is not present in the NHLBI population and was functionally validated.^{9; 10} Indeed, the *Nlgn3* knock-in mouse displayed an increase in inhibitory synaptic transmission and an “autistic-like” phenotype. Talebizadeh *et al.* identified in lymphoblastoid cells an alternative transcript of *NLGN3* that lacked exon 7 and encoded a new truncated protein, present in all 30 control individuals and in all but one of the 10 ASD females tested.¹¹ The authors speculated that the lack of the specific truncated isoform in this female might be implicated in her autistic phenotype.¹¹

To conclude, contrary to *NGLN4X* for which involvement in ASD and ID has been largely replicated in independent studies,¹²⁻¹⁴ no other mutation has been reported in *NLGN3* since 2003 in spite of a consequent number of cohorts tested (almost 700 ASD probands in total), and thus to confirm its full implication in cognitive disorders supplementary evidences are required.¹⁵⁻²⁰

***CCDC22* (coiled-coil domain-containing protein 22) : awaiting for replication**

Following expression profiling in lymphoblasts of 64 XLID subjects, a five-fold decrease in the expression of *CCDC22* mRNA was observed in one male from a large family (LOD score= 2.7), who carried the missense variant c.49A>G (p.Thr17Ala) in that gene.²¹ Although the latter variation is not present in EVS, additional evidences are obviously needed to support *CCDC22* implication in ID.

***CLIC2* (Chloride intracellular channel 2): awaiting for replication**

The re-sequencing of the X-exome in males with putative XLID allowed the detection of a variant resulting in one missense mutation in *CLIC2*.²² This variation (c.303C>G; p.His101Gln) was present in two brothers and their mother who had a low IQ. Both males presented with severe ID, seizures, atrial fibrillation, cardiomegaly and congestive heart failure. Four other non-synonymous substitutions were reported at polymorphic frequencies in this gene. The authors suggested by an *in silico* analysis that the missense mutation p.His101Gln might have an important effect on stability, dynamics and hydrogen bond network when compared to predicted effects of four missense variants found in the control population. This missense mutation was then shown to have a functional effect, activating ryanodine receptor Ca²⁺ channel, consistent with the observed cardiac phenotype.²³ This gene needs however additional evidences to be fully considered as involved in cognitive disorders.

***HCFC1* (host cell factor C1): awaiting for replication**

The mutation responsible for ID in the MRX3 family remained unsolved for a long time after the initial linkage analysis of 1991. A targeted massively parallel re-sequencing of the genomic linkage interval recently allowed the identification of a regulatory point-mutation in a functional binding site for the YY1 transcription factor in the *HCFC1* gene promoter, leading to an up-regulation of its expression in lymphoblastoid cells. Screening of additional unsolved XLID families identified at least one additional missense change c.674G>A (p.Ser225Asn) segregating with the disease in the family.²⁴ Both variations are not present in EVS, and were also described in a female with schizophrenia and a

boy with autism.²⁵ However, as *HCFC1* encodes a large protein of 2,035 amino acids, the probability to identify a missense variant in this gene is high (22 missense variants predicted as possibly or probably-damaging are detected within the NHLBI cohort). Additional evidences would therefore be useful to definitely confirm the implication of *HCFC1* in ID.

NAA10 (N-alpha-acetyltransferase 10): awaiting for replication

NAA10 was very recently reported as implicated in monogenic forms of ID, and encodes the catalytic subunit of the major human N-terminal acetyltransferase. It was identified via an X-exome sequencing strategy after selection of male probands apparently sharing the same lethal X-linked pleiotropic phenotype: aged appearance, dysmorphic features, hypotonia, developmental delay, cryptorchidism and cardiac arrhythmias.²⁶ A unique missense mutation c.109T>C (p.Ser37Pro) that fully segregated with the disease status in both unrelated families was detected. This mutation was correlated to an *in vitro* reduction of 60-80% N-terminal acetylation activity for three peptides. The catalytic subunit of the NatA complex was demonstrated to be essential for survival in several organisms. Hence, one can presume that a total loss-of-function would lead to embryonic lethality in humans, and it may also explain the early death of N-terminal acetyltransferase deficient individuals (Ogden syndrome; OGDNS: MIM# 300855) carrying the partial loss-of-function p.S37P missense mutation. A second recent study screening simplex probands with non-syndromic ID and their parents through exome sequencing allowed the detection of another *de novo* variation c.346C>T resulting in a missense change (p.Arg116Trp) in one male.²⁷ This mutation was proposed to lead to a phenotype that does not coincide with the one described in OGDNS probands, besides the large ears, hypotonia and enlarged cerebral ventricles. All male probands affected with OGDNS manifest severe developmental delay and die before the age of two. The p.Arg116Trp missense change appears less damaging than the initial p.S37P and is in fact predicted as benign by PolyPhen. The Arg116 residue is located within the acetyltransferase domain of the protein, and the authors proposed that the change into a tryptophan might lead to an interference with Coenzyme A binding and to a reduced enzymatic activity. None of these missense mutations are reported within the NHLBI population. While the implication of *NAA10* in OGDNS appears very convincing, its implication in non-syndromic ID would require additional evidence.

RPL10 (ribosomal protein L10): awaiting for replication

RPL10 was selected for reassessment of its implication in ID because only two nucleotide substitutions c.616C>A and c.639C>G have been described in males with ASD.^{28; 29} It encodes a key protein for both the assembly of the large ribosomal subunit and global protein synthesis. The resulting missense changes p.Leu206Met and p.His213Gln were detected following the sequencing of candidate genes within linked regions in 296 families with ASD and with/without associated ID, and appeared to have subtle effect on ribosomal profile in a yeast complementation assay.²⁹ The p.His213Gln missense mutation was later identified in an unrelated simplex case, inherited from a carrier mother.²⁸ Both missense variations are located at the very C-terminal end of the protein in an eukaryote-specific extension, and appear not so conserved. They are nonetheless not observed within the NHLBI population. Additional screening of 189 individuals with ASD did not lead to the identification of new *RPL10* mutations,³⁰ while mutations have been reported in individuals suffering from Leukemia.³¹ Thus, evidences clearly linking the reported *RPL10* missense mutations to the resulting ASD phenotype remain insufficient, but the fact that the same missense mutation (p.His123Gln) was observed in two independent families and is not reported within the NHLBI population is suggestive of an implication in cognitive disorders.

SHROOM4/KIAA1202 (shroom family member 4): awaiting for replication

After investigating the breakpoints of two balanced (X;autosome) translocations in unrelated females with moderate ID, *KIAA1202/SHROOM4* was pointed as a candidate for implication in ID due to its disruption in both cases.³² Another pathogenic CNV encompassing *SHROOM4* was detected in one XLID family.³³ Additional screening of 200 XLID families for structural variations or mutations in this gene revealed a single variation c.3266C>T (p.Ser1089Leu) in the linkage region of a large four-generation family that defined the Stocco dos Santos syndrome as a combination of severe ID, short stature and congenital hip luxation (MIM #300434; LOD score= 3.02).³² This mutation, absent from

over 1,000 control X-chromosomes, is not reported in EVS. A systematic re-sequencing study of the X-chromosome identified in ID individuals a recurrent in-frame insertion that was ultimately also reported in controls and six missense variants that do not seem involved in ID.² We also recently identified an inherited truncating mutation in one male with severe ID, short stature, hypotonia and dysmorphic traits (unpublished data). However, when performing segregation analyses, the variant was depicted in both unaffected brothers, therefore ruling out the pathogenicity of this variant (unpublished data). With a truncating variant observed in controls at hemizygous state, these findings do not support the implication of *SHROOM4* in cognitive disorders.

ZDHHC15, KLF8, KIAA2022, ZNF261/ZMYM3, CNKSR2 and FRMPD4

The implication of these six genes (*ZDHHC15, KLF8, KIAA2022, ZNF261/ZMYM3, CNKSR2* and *FRMPD4*) in ID relies for each of them on one single chromosomal rearrangement identified in simplex cases (**Table 2**). *ZDHHC15, KLF8, KIAA2022* and *ZNF261/ZMYM3* remain however commonly cited in XLID reviews and – with the exception of *ZNF261/ZMYM3* – are generally included in XLID diagnostic panels even though no additional cases has been published since the initial studies, more than eight years ago.³⁴⁻³⁷ Additional sequencing of *KIAA2022* and *KLF8* in 20 XLID families/20 ID male probands respectively in the initial studies failed to identify any other point mutation. More recently, duplication and deletion of two other genes, *CNKSR2* and *FRMPD4*, were described.^{38; 39} Such findings will also need to be replicated for both genes to be fully considered as confirmed genes involved in ID.

The examination of EVS for all six genes does not bring any complementary information: no truncating variations are reported within the NHLBI cohort for any of those. Three mutations in *KIAA2022* leading to partial or total loss of its expression have been recently reported (in abstract form) to be present in five individuals with a distinctive syndromic XLID (Van Maldergem *et al.*, ASHG meeting 2012). Publication of the cognate work should unambiguously prove implication of this gene in ID and/or autism.

PTCHD1 (Patched domain-containing protein 1): likely

PTCHD1 was initially considered as a potential ASD candidate when found to be disrupted via an inherited 160 kb deletion observed in dizygotic twin brothers in a large genome-wide analysis of structural variations in ASD subjects.⁴⁰ A later similar study genotyping 996 ASD probands and over a thousand controls confirmed these findings, revealing six additional males carrying deletions disrupting *PTCHD1*.⁴¹ An analogous study of the implication in ID of structural variants of the X-chromosome reported a 90 kb deletion spanning entire *PTCHD1* in one XLID family.⁴² Subsequently, two large mutation-screening strategies in cohorts of both ID and ASD individuals led to the identification of one additional deletion disrupting *PTCHD1* in two unrelated ID males,^{43; 44} and seven missense variations in six ASD and two ID probands respectively (see **Table 2**).⁴⁴ Two of them (c.217C>T; p.Leu73Phe and c.1409C>A; p.Ala470Asp) did not fully segregate with the ID status in the family. Interestingly, two out of the seven missense variations are detected among the NHLBI population: the non-segregating p.Leu73Phe is reported in one heterozygous female and the c.517A>G; p.Ile173Val in two males and two females. However, since none of the other missense mutations are reported in EVS, the expression pattern in fetal and adult brain along with the cumulative evidences through CNV and point mutation analysis in both ASD and ID probands support the implication of *PTCHD1* in cognitive disorders.

SYN1 (synapsin-1): likely

SYN1 was first suggested as a candidate for Rett syndrome (MIM# 312750) due to its proposed role in the modulation of neurotransmitter release.^{45; 46} It was later screened because it was located in the linkage region of a family with epilepsy and some learning difficulties (LOD score = 3.65) and a truncating mutation c.1197G>A (p.Trp356*) was identified, which fully segregated with the disease status.⁴⁷ Another study supported those results, with the detection of another truncating mutation in a large family with ASD, low IQ and epilepsy, and of three other missense variations (c.152C>G ; p.Ala51Gly, c.1648G>A; p.Ala550Thr, c.1699A>G; p.Thr567Ala) in additional families with similar phenotype.⁴⁸ Interestingly, the missense mutation p.A550T was detected in four unrelated individuals

with different phenotypes: one female and one male presenting with only epilepsy, one female with both epilepsy and ASD, and one male with only ASD, hence suggesting variable phenotypic expression. The missense variant p.Ala51Gly was present in one epileptic female, and in one ASD male also carrying the p.Thr567Ala variant, already suggesting one of the two variants might not contribute to the phenotype. The latter encoded p.Ala51Gly missense variant is indeed an innocuous variant since it is reported in the NHLBI population in 11 hemizygous males and 30 carrier females. Although some doubts remain about the pathogenicity of the p.Thr567Ala variant, EVS data is not informative since the corresponding region is not covered. The *SYN1* KO mouse presents a global disorganization of synaptic vesicles at presynaptic terminals, hence suggesting an important role for formation and maintenance of presynaptic structure.^{49; 50} Mice lacking synapsin 1 exhibit epileptic seizures and cognitive impairment with aging consistent with the suggested human disease phenotype.^{49; 51}

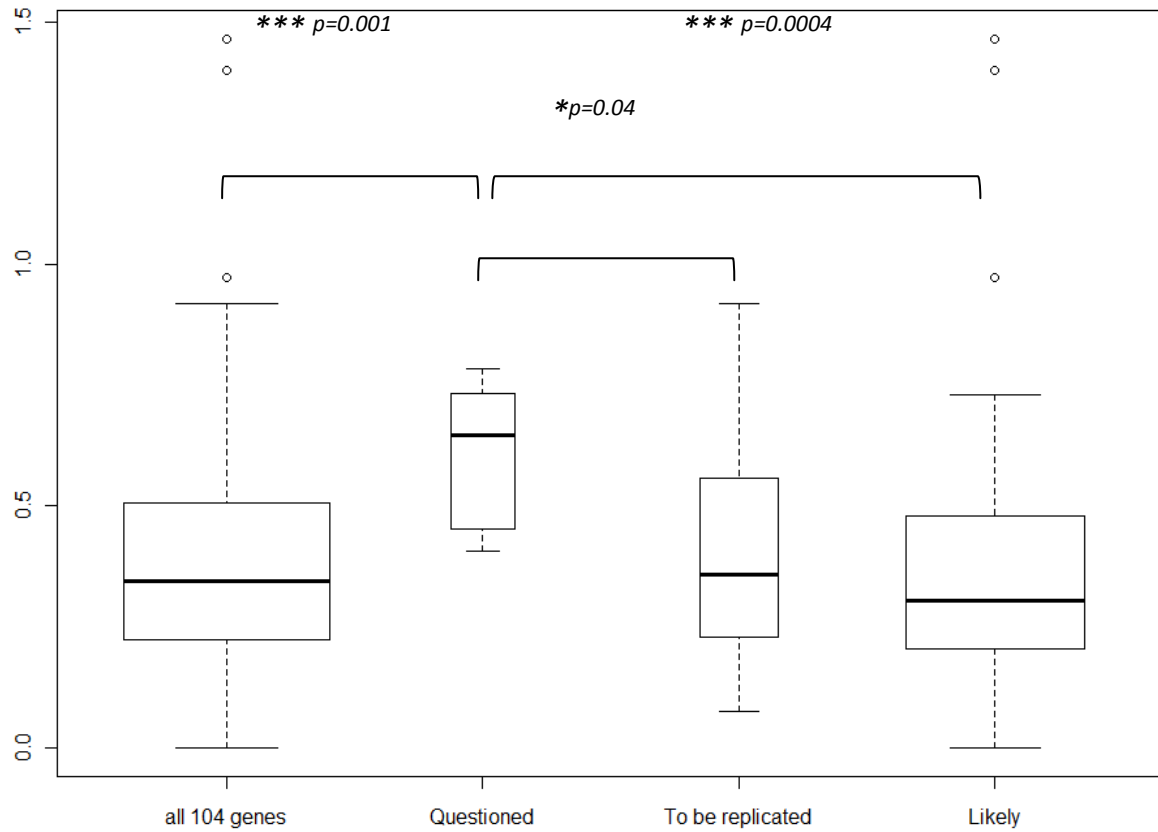


Figure S1. Distribution of the Computed dN/dS Ratios for All 104 Selected Genes and by Category, according to Their Putative Association with Intellectual Disability When Mutated

The dN/dS ratios distribution is compared between several categories: all genes, the 10 genes whose association in ID is questioned, the 15 genes which need to be replicated and the remaining genes with consistent association with monogenic forms of ID when mutated. The boxplot was generated in R: the width of all boxes are proportional to $\sqrt{(\text{number of values})}$. Circles represent outliers ranging outside of the interval whiskers, which extend up to $1.5 \times (3^{\text{rd}} \text{ quartile} - 1^{\text{st}} \text{ quartile})$. Significance levels between all gene subsets are computed using a Student's t-test with unequal variances in R.

Table S1. Catalog of Single Nucleotide Truncating Variants Reported among the EVS Population in All Selected Genes, Supposedly Implicated in XLID When Mutated

Gene (transcript#)	Lists	Truncating variant (p./protein length)	Truncating variant (c.)	Variant occurrence (: #X-chr)	#Males (hemz)	#Females (htz)	Comments
<i>AGTR2</i> (NM_000686.4)	L, R, G, E, A	p.Trp158* (/364)	c.474G>A	1:10,563	-	1 F	
<i>ATP6AP2</i> (NM_005765.2)	L, R, G, E, A	splice variant (g.X:40464811)	c.859-2A>C	1:10,559	1 M	-	one isoform uses an alternative AG for this exon
<i>ATRX</i> (NM_000489.3)	L, R, G, E, A	p.Leu1022* (/2455)	c.3065A>C	1:10,545	-	1 F	-
<i>BCOR</i> (NM_001123385.1)	L, R, G, E, A	splice variant (g.X:39922860; <i>rs147281758</i>)	c.3847+1C>G	1:10,561	-	1 F	-
<i>DLG3</i> (NM_020730.2)	L, R, G, E, A	p.Trp24* (/513)	c.71G>A	1:9,797	1 M	-	affects only isoform#2 (NM_020730.2)
<i>DMD</i> (NM_004006.2)	L, R, G, E	p.Trp3416* (/3686)	c.10247C>T	2:10,560	-	2 F	
		splice variant (g.X:31196048; <i>rs145603325</i>)	c.10262+1C>T	6:10,561	-	6 F	
		splice variant (g.X:32429867; <i>rs147474070</i>)	c.4233+2G>A	3:10,561	1 M	2 F	
		splice variant (g.X:32591646)	c.1812+1C>T	1:10,558	-	1 F	
<i>MAGT1</i> (NM_032121.5)	L, R, G, E	p.Ser24* (/368)	c.71G>C	1:10,558	1 M	-	
<i>NXF5</i> (NM_032946.2)	L, R, G, A	p.Arg320* (/366) <i>rs140252282</i>	c.958G>A	33:10,563 (MAF=0,31%)	7 M	26 F	-
		p.Cys54* (/366)	c.162G>T	1:10,563	1 M	-	-
<i>OFD1</i> (NM_003611.2)	L, R, G, E, A	splice variant (g.X:13769366)	c.936-2A>G	1:10,554	1 M	-	exon not present in all isoforms
<i>SHROOM4</i> (NM_020717.3)	L, R, G, E, A	p.Trp128* (/1494) <i>rs142159861</i>	c.383C>T	1:10,563	-	1 F	
<i>SLC9A6</i> (NM_001042537.1)	L, R, G, E, A	splice variant (g.X:135095107; <i>rs149044510</i>)	c.1042-1C>T	1:10,563	-	1 F	-
<i>UPF3B</i> (NM_080632.2)	L, R, G, E	splice variant (g.X:118974608)	c.846+1C>T	1:10,563	-	1 F	
<i>ZNF41</i> (NM_007130.2)	L, R, G, E, A	splice variant (g.X:47315319; <i>rs143323743</i>)	c.295+1C>T	1:10,563	1 M	-	-
		p.Trp41* (/780)	c.122C>T	1:10,563	-	1 F	-
<i>ZNF674</i> (NM_001039891.2)	L, R, E, A	p.Asp442* (/582)	c.1324C>A	5:10,509	-	5 F	
		p.Arg201* (/582)	c.601G>A	44:9,514 (MAF=0,46%)	19 M	25 F	
<i>ZNF81</i> (NM_007137.3)	L, R, G, E, A	p.Lys384* (/662)	c.1150A>T	1:10,533	1 M	-	

XLID lists in which genes are included: L=Lubs et al.,⁵² R=Ropers et al.,⁵³ G=Greenwood, E=Emory, A=Ambry. When a variant is reported in dbSNP137, the subsequent identifier is indicated in italic (*rs#*). Gender of control individuals carrying the variant: M: Male, F: Female.

Table S2. List of XLID Mutations Reported in OMIM and in Literature for the 104 Selected Genes (*Additional Mutations from the Literature Only)

Gene	Mutation
ABCD1	GLU291LYS
ABCD1	PRO484ARG
ABCD1	IVS6AS, A-G, c.1635-2, g.153006026
ABCD1	IVS8AS, G-A, -10, 8-BP INS
ABCD1	ARG389GLY
ABCD1	ASN148SER
ABCD1	TYR174ASP
ABCD1	GLY266ARG
ABCD1	ARG401GLN
ABCD1	ARG418TRP
ABCD1	ARG464TER
ABCD1	2-BP DEL, 1801AG
ABCD1	GLU477TER
ABCD1	SER515PHE
ABCD1	1-BP DEL, 1937C
ABCD1	ARG518TRP
ABCD1	IVS6DS, G-A, g.153005692, c.1634+1
ABCD1	2-BP DEL, 2177TA
ABCD1	SER606LEU
ABCD1	1-BP DEL, 2204G
ABCD1	ARG617HIS
ABCD1	ARG617CYS
ABCD1	3-BP DEL, 1258GAG, GLU291DEL
ABCD1	IVS8DS, G-A, c.1865+1, g.153008526
ABCD1	IVS1DS, G-A, c.901-1, g.152994686
ABCD1	26-BP DEL, NT369
ACSL4	ARG529SER
ACSL4	IVS10, A-G, -2
ACSL4	PRO375LEU
AFF2	(GCC) _n EXPANSION
AFF2	121- to 145-KB DEL
AGTR2	GLY21VAL
AGTR2	1-BP DEL, 395T
AGTR2	ARG324GLN
AGTR2	ILE337VAL
AGTR2	ILE53PHE
AP1S2	GLN36TER
AP1S2	ARG52TER
AP1S2	4-BP DEL, NT180
AP1S2	IVS3DS, G-A, +5
AP1S2	GLN66TER
ARHGEF6	IVS1AS, T-C, -11
ARHGEF9	GLY55ALA
ARHGEF9	GLN2TER
ARX	(GCG) ₁₀₊₇

ARX, 24-BP DUP, NT428
ARX, PRO353LEU
ARX, 1,517-BP DEL
ARX, 32-BP DEL, NT420
ARX, 1-BP DEL, 790C
ARX, ARG332HIS
ARX, GLN373TER
ARX, 1-BP INS, 1188C
ARX, EX1-2DEL
ARX, 1-BP DEL, 1372G
ARX, LEU343GLN
ARX, LEU33PRO
ARX, GLY286SER
ARX, THR333ASN
ARX, GLU369TER
ARX, 33-BP DUP
ARX, 24-BP DEL, NT441
ARX, 1-BP DEL, 617G
ARX, GLU78TER
ARX, 1-BP DEL, 1465G
ARX, 27-BP DUP, NT430
ARX, TYR27TER
ARX, LEU535GLN
ATP6AP2, ASP107ASP
ATP7A, IVSXDS, A-T, +3
ATP7A, IVSAS, 2642A-G, -2
ATP7A, SER637LEU
ATP7A, 8-BP DEL, NT1552
ATP7A, ARG980TER
ATP7A, IVS6DS, T-A, +6
ATP7A, IVS6DS, G-A, +1
ATP7A, 1-BP DEL, 4497G
ATP7A, GLY1019ASP
ATP7A, EX8 DEL
ATP7A, 8-BP DEL, NT408
ATP7A, EX3-4 DEL
ATP7A, ASN1304SER
ATP7A, ARG201TER
ATP7A, THR994ILE
ATP7A, PRO1386SER
ATRX, HIS750ARG
ATRX, CYS755ARG
ATRX, LYS792ASN
ATRX, ASN1002SER
ATRX, ASP1177VAL
ATRX, TYR1226HIS
ATRX, TYR1305CYS
ATRX, ARG1528TER
ATRX, GLU1530TER

ATRX, IVSAS, T-A, -10
ATRX, ARG1272GLN
ATRX, PRO852SER
ATRX, 751A-G
ATRX, PRO73ALA
ATRX, ARG129CYS
ATRX, ARG1742LYS
ATRX, IVS34, A-G, -2
ATRX, ARG246CYS
ATRX, THR1621MET
ATRX, IVS1DS, G-A, +1
ATRX, SER79TER
ATRX, ARG37TER
ATRX, LEU409SER
ATRX, ILE2052THR
ATRX, CYS220TYR
ATRX, ARG2271GLY
BCOR, PRO85LEU
BCOR, IVS8AS, G-T, -1
BCOR, ARG976TER
BCOR, 1-BP DEL, 3881A
BCOR, EX9-15DEL
BCOR, 2-BP DEL, 2488AG
BCOR, 1-BP DEL, 3286G
BCOR, 60-KB DEL
BCOR, 1-BP DEL, 1315C
BRWD3, IVS29, G-T, +1
BRWD3, 1-BP INS, 946A
BRWD3, LYS1596GLU
CASK, ARG639TER
CASK, 915G-A, EX9
CASK, ARG28LEU
CASK, TYR268HIS
CASK, ASP710GLY
CASK, TRP914ARG
CASK, PRO396SER
CASK, TYR728CYS
CASK, IVS25AS, A-T, -2
CASK, ARG106TER
CASK, 100-KB DEL
CASK, GLN547TER
CCDC22, THR17ALA
CDKL5, 1-BP DEL, 183T
CDKL5, IVSAS13, G-A, -1
CDKL5, CYS152PHE
CDKL5, ARG175SER
CDKL5, 4-BP DEL, 166GAAA
CDKL5, 2-BP DEL, 2636CT
CDKL5, GLN834TER

CDKL5, IVS6AS, G-T, -1
CDKL5, ALA40VAL
CDKL5, ILE72THR
CDKL5, THR288ILE
CDKL5, CYS291TYR
CDKL5, 2-BP INS, 903GA
CDKL5, ARG178PRO
*CLIC2, HIS101GLN
CUL4B, c.1007_1011delTTATA, p.I336fs*2
CUL4B, ARG572CYS
CUL4B, ARG388TER
*CUL4B, THR831THR
*CUL4B, R856TER
CUL4B, IVS6, A-G, -2
*CUL4B, IVS7, A-G, -2
*CUL4B, VAL745ALA
DCX, ASP62ASN
DCX, ARG192TRP
DCX, TYR125HIS
DCX, IVS4, G-A, +1
DCX, ARG59LEU
DCX, THR203ARG
DCX, SER47ARG
DCX, 2-BP INS, 36AG
DCX, 2-BP DEL, 684CT
DCX, 2-BP DEL, 691CT
DCX, ARG78HIS
DCX, ARG89GLY
DCX, ARG196HIS
DCX, ALA71SER
DKC1, PHE36VAL
DKC1, LEU37DEL
DKC1, PRO40ARG
DKC1, LEU72TYR
DKC1, GLY402GLU
DKC1, ALA353VAL
DKC1, 2-KB DEL
DKC1, -141C-G
DKC1, IVS1, C-G, +592
DKC1, THR49MET
DKC1, SER121GLY
DKC1, ILE38THR
DKC1, GLN31LYS
DKC1, THR357ALA
DKC1, IVS12DS, G-A, +1
DLG3, IVS6DS, G-A, +5
DLG3, IVS8DS, G-A, +1
DLG3, 1-BP INS, 1325C
DLG3, SER458TER

DMD, GLU1157TER
DMD, PROMOTER DEL
DMD, GLU931TER
DMD, GLN1851TER
DMD, ARG2982TER
DMD, IVS68, T-A, +2
DMD, ARG3370TER
DMD, EX73-76DEL
DMD, 1-BP DEL, 10662T
DMD, 1-BP INS, EX12
DMD, AG-T, EX48
DMD, EX21DEL
DMD, EX18DEL
DMD, GLN2319TER
DMD, ARG768TER, C-T, NT2510
DMD, 1-BP DEL, 2568C
DMD, GLU772TER, G-T, NT2522
DMD, IVS19, A-C, +3
DMD, IVS57, G-C, -1
DMD, LEU54ARG
DMD, EX1DEL
DMD, IVS26, T-G, +2
DMD, GLN673TER
DMD, 1-BP DEL, 10334C AND IVS69, G-T, +1
DMD, IVS1, G-T, +1
DMD, CYS3340TYR
DMD, IVS2, G-T, -1
DMD, 2-BP DEL, 382AG
DMD, GLN60TER
DMD, 1-BP INS, 402A
DMD, GLN85TER
DMD, ARG145TER
DMD, ALA168ASP
DMD, 1-BP DEL, 724C
DMD, TYR231ASN
DMD, GLN242TER
DMD, GLU250TER
DMD, 11-BP DEL, NT989
DMD, 1-BP INS, NT1554
DMD, GLY480TER
DMD, GLN497TER
DMD, TRP651TER
DMD, LYS770TER
DMD, LYS773GLU
DMD, 52-BP DEL
DMD, 1-BP INS, NT2928
DMD, GLN1041TER
DMD, TRP1063TER
DMD, GLN1405TER

DMD, GLN1472TER
DMD, ARG1967TER
DMD, 1-BP DEL, 6408C
DMD, ARG2098TER
DMD, GLN2125TER
DMD, 17-BP DEL, NT6982
DMD, GLN2264TER
DMD, 1-BP INS, 7188A
DMD, IVS47, G-A, +1, EX48DEL
DMD, GLU2468TER
DMD, GLU2910VAL
DMD, ASN2912ASP
DMD, HIS2921ARG
DMD, SER3066TER
DMD, 4-BP DEL, NT9679
DMD, IVS65, G-A, +1
DMD, ARG3381TER
DMD, IVS70, G-A, +1
DMD, IVS70, G-T, +5
DMD, ALA3421VAL
DMD, 1-BP DEL, 10683C
DMD, 8-BP DEL, 1-BP INS, NT10692
DMD, THR279ALA
DMD, GLU1211TER, 3839G-T
DMD, ALU INS
DMD, ARG3190TER
DMD, ARG1314TER
DMD, 1-BP DEL, 377A
DMD, 16-BP DEL
DMD, IVS62, A-G, -285
DMD, IVS25, A-G, +2036
DMD, ARG2905TER
DMD, IVS2, T-A, +5591
DMD, TYR1995TER
DMD, EX45-47DEL
DMD, TRP3TER
FANCB, 1-BP INS, 1838T
FANCB, 3314-BP DEL
FANCB, 1-BP DEL, 1650T
FANCB, 1-BP INS, 811T
FANCB, IVS7DS, G-A, +5
FANCB, LEU717TER
FANCB, 2-BP DEL, 1857AG
FGD1, 1-BP INS, 2122G
FGD1, ARG610GLN
FGD1, ARG522HIS
FGD1, EX9-12DEL
FGD1, PRO312LEU
FGD1, 1-BP INS, 528C

FGD1, ARG408GLN
FGD1, 1-BP DEL, 2189A
FGD1, ARG433LEU
FGD1, 1-BP INS, 945C
FGD1, MET466VAL
FGD1, ARG656TER
FLNA, GLN182TER
FLNA, IVS4DS, T-C, +2
FLNA, IVS3AS, C-G, -3
FLNA, IVS2DS, G-A, +1
FLNA, 5-BP DEL, NT287
FLNA, LEU656PHE
FLNA, 5915C-G
FLNA, GLU82VAL
FLNA, PRO207LEU
FLNA, GLU254LYS
FLNA, ASP1159ALA
FLNA, ALA1188THR
FLNA, SER1199LEU
FLNA, 7315C-A
FLNA, SER1186LEU
FLNA, 9-BP DEL, NT4904
FLNA, 1-BP DEL, 2762G
FLNA, 1-BP DEL, 4147G
FLNA, ALA39GLY
FLNA, ASP203TYR
FLNA, ALA128VAL
FLNA, GLY1728CYS
FLNA, 1923C-T
FLNA, 2-BP DEL, 65AC
FLNA, ARG196TRP
FLNA, CYS210PHE
FLNA, PRO1291LEU
FLNA, 5217G-A, 48-BP DEL
FLNA, PRO637GLN
FLNA, GLY288ARG
FLNA, VAL711ASP
FLNA, 1,944-BP DEL
FLNA, TRP2632TER
FMR1, ILE304ASN
FMR1, 1-BP DEL, 373A
FMR1, IVS2AS1, G-T, -1 AND G-A, +1
FMR1, (CGG)_n EXPANSION
FMR1, SER27TER
FTSJ1, EX9DEL
FTSJ1, 196C-T
FTSJ1, IVS2, G DEL, +1
FTSJ1, IVS3AS, A-G, -2
GDII, LEU92PRO

GDI1, ARG70TER
GDI1, ARG423PRO
GDI1, 2-BP DEL, 1185AG
GK, IVS6AS, G-C, -1
GK, EX17DEL
GK, ASP440VAL
GK, 20-KB DEL
GK, ARG413TER
GK, TRP503ARG
GK, ALU INS, IVS4
GK, ASN288ASP
GPC3, 13-BP DEL, NT391
GPC3, EX7DEL
GPC3, TRP296ARG
GPC3, IVS5, G-T, +1
GPC3, ARG199TER
GPC3, HIS558TYR
GPC3, ALA1902THR
GPC3, EX6DEL
GPC3, IVS2, G-A, +1
GPC3, ARG387TER
GPC3, GLY556ARG
GRIA3, GLY833ARG
GRIA3, ARG631SER
GRIA3, MET706THR
GRIA3, 0.4-MB DEL
HCCS, 8.6-KB DEL
HCCS, ARG197TER
HCCS, ARG217CYS
HCFC1, 455A-G
HCFC1, SER225ASN
HDAC8, IVS1DS, 164+5G-A
HDAC8, ARG164TER
HDAC8, HIS180ARG
HDAC8, THR311MET
HDAC8, GLY320ARG
HDAC8, HIS334ARG
HPRT, ILE132MET
HPRT, ASP80VAL
HPRT, ASP201GLY
HPRT, 1-BP INS, 56T
HPRT, EX8DEL
HPRT, LEU41PRO
HPRT, 24AA+
HPRT, PHE74LEU
HPRT, ASP194ASN AND ASP193ASN
HPRT, SER110LEU
HPRT, 3-BP DEL, VAL179DEL
HPRT, VAL130ASP

HPRT, ALA161SER
HPRT, SER104ARG
HPRT, PHE199VAL
HPRT, GLY70GLU
HPRT, GLY71ARG
HPRT, GLN108TER
HPRT, HIS203ASP
HPRT, ARG44LYS
HPRT, ASP176TYR
HPRT, 2-BP DEL, GT
HPRT, 1-BP DEL, TTA-TA
HPRT, 1-BP DEL, TTG-TG
HPRT, 40-BP DEL
HPRT, IVS8DS, G-A, +5
HPRT, IVS8AS, ATAG-TTTG
HPRT, IVS7DS, G-A, +5
HPRT, IVS1AS, A-T, -2
HPRT, PRO176LEU
HPRT, ARG51GLY
HPRT, ARG51TER
HPRT, MET56THR
HPRT, MET143LYS
HPRT, ARG170TER
HPRT, 13-BP DEL, 5-PRIME UTR
HPRT, EX2DEL
HPRT, EX4-9DEL
HPRT, EX6-9DEL
HPRT, EX9DEL
HPRT, DEL
HPRT, INV/DEL, EX6-9
HPRT, EX2-3DUP, IVS1DEL
HPRT, THR168ILE
HPRT, GLY16SER
HPRT, GLY58ARG
HPRT, LEU78VAL
HPRT, EX6DEL
HPRT, 1-BP INS, 14823T
HPRT, ASP52GLY
HPRT, GLY140ASP
HPRT, ASP194GLU
HPRT, TYR153TER
HPRT, 2969-BP DEL, NT970
HPRT, LEU65PHE
HPRT, ARG48HIS
HSD17B10, ARG130CYS
HSD17B10, LEU122VAL
HSD17B10, ASN247SER
HSD17B10, ARG192ARG
HSD17B10, GLU249GLN

HUWE1, ARG4013TRP
HUWE1, ARG2981HIS
HUWE1, ARG4187CYS
*HUWE1, VAL950ASP
*HUWE1, DUP
IDS, ARG443TER
IDS, SER333LEU
IDS, TRP502SER
IDS, PRO160ARG
IDS, ARG172TER
IDS, 60-BP DEL, NT1244
IDS, DEL
IDS, CYS422GLY
IDS, LYS135ARG
IDS, TRP475TER
IDS, 2-BP DEL, CODON 170
IDS, ARG468TRP
IDS, ARG468GLN
IDS, 78-BP INS
IDS, ARG468LEU
IDS, 3-BP DEL, 473TCC
IDS, GLY489ALA, MET488ILE
IGBP1, -57delT and -55T-A, 5-PRIME UTR
IKBKG, EXON 4-10 DEL
IKBKG, TER420TRP
IKBKG, 10-BP INS, NT127
IKBKG, 1-BP INS, 1110C
IKBKG, MET407VAL
IKBKG, PRO62TER
IKBKG, GLU391TER
IKBKG, 1-BP DUP, 1167C
IKBKG, CYS417ARG
IKBKG, CYS417PHE
IKBKG, ASP406VAL
IKBKG, 13-BP DUP, NT1166
IKBKG, 4.4-KB DUP
IKBKG, LEU153ARG
IKBKG, GLN403TER
IKBKG, IVS6DS, G-A, +5
IKBKG, 1-BP INS, 1409A
IKBKG, IVS8, -1, G-A
IKBKG, 1-BP INS, 110C
IKBKG, ALA288GLY
IKBKG, GLU315ALA
IKBKG, ARG319GLN
IKBKG, 518C-G, ARG173GLY
IL1RAPL1, TYR459TER
IL1RAPL1, TRP487TER
IL1RAPL1, EX2-5DEL

IL1RAPL1, 730-KB DEL, EX3-7
IQSEC2, ARG863TRP
IQSEC2, GLN801PRO
IQSEC2, ARG758GLN
IQSEC2, ARG359CYS
IQSEC2, ARG855TER
KDM5C, LEU731PHE
KDM5C, 1-BP INS, 202C
KDM5C, ALA388PRO
KDM5C, ARG694TER
KDM5C, SER451ARG
KDM5C, ARG766TRP
KDM5C, ALA77THR
KDM5C, CYS724TER
KDM5C, PRO554THR
SHROOM4, SER1089LEU
*SHROOM4, GLU474GLU
L1CAM, IVS18AS, A-C, -19
L1CAM, CYS264TYR
L1CAM, 1.3-KB DUP
L1CAM, HIS210GLN
L1CAM, ASP598ASN
L1CAM, GLY452ARG
L1CAM, ARG184GLN
L1CAM, 2-BP DEL, EX26
L1CAM, SER1194LEU
L1CAM, ILE179SER
L1CAM, GLY370ARG
L1CAM, 2-BP DEL, EX18
L1CAM, 924C-T
L1CAM, VAL752MET
L1CAM, IVS15DS, G-A, +5
L1CAM, GLN974TER
L1CAM, PRO240LEU
L1CAM, IVS26AS, G-C, -1
LAMP2, 2-BP DEL, 1097AA
LAMP2, LEU113TER
LAMP2, IVS6, G-C, +5
LAMP2, 1-BP INS, 974A
LAMP2, IVS5, G-A, +1
LAMP2, 1-BP DEL, 14G
LAMP2, 1-BP INS, 883T
LAMP2, 7-BP DEL
LAMP2, GLN174TER
LAMP2, VAL310ILE
LAMP2, TRP321ARG
LAMP2, 1-BP DEL, 1219A
MAGT1, VAL343GLY
MAOA, GLN296TER

MAOA, PROMOTER POLYMORPHISM, 30-BPREPEAT

MBTPS2, HIS277LEU

MBTPS2, MET87ILE

MBTPS2, ARG429HIS

MBTPS2, PHE475SER

MBTPS2, TRP226LEU

MBTPS2, ARG508SER

MECP2, ARG133CYS

MECP2, PHE155SER

MECP2, 1-BP DEL, 806G

MECP2, 44-BP DEL, NT1152

MECP2, ARG270TER

MECP2, IVS2, A-G, -2

MECP2, THR158MET

MECP2, ARG106TRP

MECP2, GLU406TER

MECP2, 2-BP DEL, 211CC

MECP2, ARG294TER

MECP2, 41-BP DEL, NT1157

MECP2, 41-BP DEL, NT1159

MECP2, 44-BP DEL, NT1159

MECP2, ALA140VAL

MECP2, ARG306CYS

MECP2, GLU137GLY

MECP2, 1-BP DEL, 76C

MECP2, 14-BP DUP, NT766

MECP2, ARG168TER

MECP2, ARG255TER

MECP2, 240-BP DEL, NT1161

MECP2, GLY428SER

MECP2, 52-BP DEL

MECP2, TYR141TER

MECP2, GLU455TER

MECP2, LEU100VAL

MECP2, 11-BP DEL, EX1

MECP2, 5-BP DUP, EX1

MECP2, DUP

MECP2, 1-BP DEL AND 2-BP INS

MECP2, 2-BP DEL, 488GG

MECP2, PRO225LEU

MECP2, 32-BP DEL, NT1154

MECP2, PRO322SER

MECP2, PRO152ALA

MECP2, ALA2VAL

MECP2, 1-BP DEL, 710G

MED12, ARG961TRP

MED12, ASN1007SER

*MED12, ARG1148HIS

*MED12, SER1165PRO

*MED12 , HIS1729ASN
MID1, 3-BP DEL, MET438
MID1, 24-BP DUP
MID1, 1-BP INS
MID1, LEU626PRO
MID1, GLU115TER
MID1, EX1 DUP
MID1, LEU295PRO
MID1, 2-BP DEL, 1545GA
MID1, GLU238TER
NAA10, SER37PRO
*NAA10, ARG116TRP
NDP, ARG90PRO
NDP, SER75CYS
NDP, VAL60GLU
NDP, TYR44CYS
NDP, CYS96TYR
NDP, LEU124PHE
NDP, CYS69SER
NDP, CYS128TER
NDP, MET1VAL
NDP, ARG121TRP
NDP, LEU13ARG
NDP, LEU61PHE
NDP, HIS42ARG
NDP, 1-BP DEL
NDP, ALA105THR
NDP, CYS110GLY
NDP, ARG121LEU
NDP, CYS96TRP
NDP, VAL45GLU
NDP, SER73TER
NDP, SER101PHE
NDUFA1, GLY8ARG
NDUFA1, ARG37SER
NDUFA1, GLY32ARG
NHS, 1-BP INS, 2387C
NHS, 1-BP DEL, 3459C
NHS, ARG378TER
NHS, 1-BP INS, 718G
NHS, GLN39TER
NHS, IVS3AS, A-G, -2
NHS, 500-KB TRIPLICATION
NHS, 4.8-KB DEL
NLGN3, ARG451CYS
NLGN4, 1-BP INS, 1186T
NLGN4, 2-BP DEL, 1253AG
NLGN4, 757-KB DEL
NSDHL, ALA105VAL

NSDHL, GLY205SER
NSDHL, GLN210TER
NSDHL, ARG88TER
NSDHL, ALA182PRO
NSDHL, GLU151TER
NSDHL, 1-BP DUP, 1098T
NSDHL, 3-BP DEL, 696GAA
OCRL, 112-BP DEL
OCRL, ARG-TER
OCRL, ARG577GLN
OCRL, HIS601GLN
OCRL, TYR462CYS
OCRL, ARG301CYS
OCRL, ARG476TRP
OCRL, ILE526THR
OCRL, 2-BP DEL, 166TT
OFD1, SER434ARG
OFD1, 1-BP DEL, 312G
OFD1, 19-BP DEL, NT294
OFD1, IVS5AS, T-G, -10
OFD1, 2-BP INS, 1887AT
OFD1, 4,094-BP DEL, 14-BP DEL
OFD1, 4-BP DUP, 2122AAGA
OFD1, 7-BP DEL, NT2841
OFD1, 1-BP DEL, 2767G
OFD1, 18-BP DEL, EX 8
OPHN1, 1-BP DEL, NT1578
OPHN1, 8-BP DUP
OPHN1, GLN62TER
OPHN1, 17.6-KB DEL
OPHN1, 2-BP DEL, NT642
OPHN1, 68-KB DEL
OTC, DEL
OTC, ARG109GLN
OTC, ARG109TER
OTC, LEU111PRO
OTC, GLN216GLU
OTC, GLU154TER
OTC, LEU45PRO
OTC, ARG26GLN
OTC, LYS46ARG
OTC, ARG245TRP
OTC, GT-GC, INTRON 7
OTC, GTA-GTG, INTRON 7
OTC, IVS4, A-T, -2
OTC, ARG277TRP
OTC, PRO225LEU
OTC, GLU87LYS
OTC, GLY50TER

OTC, GLY162ARG
OTC, 1-BP DEL, 403G
OTC, IVS2, G-A, -1
OTC, GLY47GLU
OTC, ARG62THR
OTC, LEU272PHE
OTC, TYR313ASP
OTC, ARG129HIS
OTC, LEU148PHE
OTC, MET206ARG
OTC, ARG40CYS
OTC, ARG40HIS
PAK3, ARG419TER
PAK3, ARG67CYS
PAK3, ALA365GLU
PAK3, TRP446SER
PAK3, IVS6DS, A-G, +4
PCDH19, 1-BP INS, 1091C
PCDH19, VAL441GLU
PCDH19, GLN85TER
PCDH19, SER671TER
PCDH19, 1-BP INS, 2030T
PCDH19, GLU48TER
PCDH19, 5-BP DUP, NT1036
PCDH19, ASN557LYS
PDHA1, 4-BP DEL
PDHA1, 7-BP DEL
PDHA1, ARG378HIS
PDHA1, LYS313DEL
PDHA1, 2-BP DEL
PDHA1, 20-BP DEL, EX11DEL
PDHA1, 21-BP INS
PDHA1, ARG234GLY
PDHA1, ARG302CYS
PDHA1, 4-BP INS, 1251ACTA
PDHA1, ASP258ALA
PDHA1, PHE205LEU
PDHA1, TYR243ASN
PDHA1, ASP315ASN
PDHA1, MET282LEU
PDHA1, 1-BP INS, FS141TER
PDHA1, ARG10PRO
PDHA1, 13-BP INS, EX10
PDHA1, 36-BP INS
PDHA1, ARG288HIS
PDHA1, 12-BP INS, EX11
PDHA1, ARG263GLY
PDHA1, LEU216PHE
PGK1, ASP268ASN

PGK1, ARG206PRO
PGK1, VAL266MET
PGK1, THR352ASN
PGK1, LEU88PRO
PGK1, GLY157VAL
PGK1, CYS315ARG
PGK1, 3-BP DEL, LYS191DEL
PGK1, ILE252THR
PGK1, ASP285VAL
PGK1, ILE46ASN
PGK1, SER319ASN
PGK1, ASP164VAL
PGK1, IVS7DS, G-A, +5
PGK1, THR378PRO
PHF6, ARG342TER
PHF6, CYS99PHE
PHF6, LYS234GLU
PHF6, CYS45TYR
PHF6, HIS229ARG
PHF6, MET1TYR
PHF6, ARG257GLY
PHF6, LYS8TER
PHF6, IVS2AS, A-G, -8
PHF6, 1-BP INS, 27A
PHF8, 12-BP DEL
PHF8, ARG211TER
PHF8, LYS177TER
PHF8, PHE279SER
PLP1, PRO215SER
PLP1, TRP162ARG
PLP1, PRO14LEU
PLP1, THR155ILE
PLP1, VAL218PHE
PLP1, DEL
PLP1, THR181PRO
PLP1, LEU223PRO
PLP1, ASP202HIS
PLP1, GLY73ARG
PLP1, GLY220CYS
PLP1, HIS139TYR
PLP1, ILE186THR
PLP1, THR42ILE
PLP1, MET1ILE
PLP1, -34C-T, 5-PRIME UTR
PLP1, PHE236SER
PLP1, TRP144TER
PLP1, ALA242VAL
PLP1, SER169PHE
PLP1, DUP

PLP1, IVS6DS, G-T, +3
PLP1, IVS3DS, T-C, +2
PLP1, IVS3DS, A-G, +4
PLP1, IVS3, 19-BP DEL, +28
PLP1, ARG137TRP
PLP1, ASP57TYR
PORCN, 13-BP DUP, NT1059
PORCN, 178G-A, GLY60ARG
PORCN, ARG124TER
PORCN, TRP74TER
PORCN, ARG365GLN
PQBP1, 2-BP INS, 3900AG
PQBP1, 4-BP DEL, 3896AGAG
PQBP1, 2-BP DEL, 3898AG
PQBP1, 1-BP INS, 641C
PQBP1, 23-BP DEL, NT547
PQBP1, 21-BP DEL, NT334
PQBP1, TYR65CYS
PRPS1, ASN113SER
PRPS1, ASP182HIS
PRPS1, ASP51HIS
PRPS1, LEU128ILE
PRPS1, ALA189VAL
PRPS1, HIS192GLN
PRPS1, GLU43ASP
PRPS1, MET115THR
PRPS1, LEU152PRO
PRPS1, GLN133PRO
PRPS1, ASP65ASN
PRPS1, ALA87THR
PRPS1, GLY306ARG
PRPS1, ILE290THR
PRPS1, VAL142LEU
*PTCHD1, I173V
*PTCHD1, ML336-7II
*PTCHD1, E479G
*PTCHD1, L73F
*PTCHD1, A470D
*PTCHD1, H359R
*PTCHD1, V195I
RAB39B, IVS1DS, G-A, +1
RAB39B, TYR7TER
RBM10, 1-BP INS, 1893A
RBM10, TRP412TER
RPL10, LEU206MET
RPL10, HIS213GLN
RPS6KA3, 187-BP DEL, NT406
RPS6KA3, GLY75VAL
RPS6KA3, SER227ALA

RPS6KA3, VAL82PHE
RPS6KA3, IVS4AS, G-C, -1
RPS6KA3, ARG114TRP
RPS6KA3, 2-BP DEL, 451AG
RPS6KA3, GLN689TER
RPS6KA3, ARG729GLN
RPS6KA3, ARG383TRP
RPS6KA3, ILE189LYS
RPS6KA3, IVS6, A-G, +3
RPS6KA3, IVS5, A-G, -11
RPS6KA3, 1-BP DEL, 2144C
RPS6KA3, IVS12, A-G, -2
RPS6KA3, IVS3, L1 INS, -8
RPS6KA3, PHE268SER
RPS6KA3, 3-BP DEL, 1428TAT
RPS6KA3, DUP EXONS 17-20, NT1959
RPS6KA3, 3-BP DEL, 454GGA
RPS6KA3, THR115SER
*SIZN1, ARG7CYS
*SIZN1, THR344ILE
SLC16A2, LEU512PRO
SLC16A2, 1-BP DEL, 1212T
SLC16A2, ALA224VAL
SLC16A2, EX1DEL
SLC16A2, LEU397PRO
SLC16A2, 2.4-KB DEL
SLC16A2, LEU568PRO
SLC16A2, LEU434TRP
SLC16A2, SER448TER
SLC16A2, PHE230 DEL
SLC16A2, 1-BP DEL, 1834C
SLC6A8, ARG514TER
SLC6A8, GLY381ARG
SLC6A8, 3-BP DEL, 1221TTC
SLC6A8, 1-BP INS, 950A
SLC6A8, GLY87ARG
SLC6A8, IVS1AS, A-G, -2
SLC6A8, CYS337TRP
SLC6A8, GLY132VAL
SLC6A8, CYS491TRP
SLC6A8, 3-BP DEL, 1006AAC
SLC9A6, 6-BP DEL, NT764
SLC9A6, ARG468TER
SLC9A6, IVS3, AA-CC
SLC9A6, 2-BP DEL, 511_512delAT
SLC9A6, 9-BP DEL, NT1012
SMC1A, 3-BP DEL, 2493CCA
SMC1A, GLU493ALA
SMC1A, 15-BP DEL, NT173

SMC1A, ARG496HIS
SMC1A, ILE784THR
SMC1A, 8.152-KB DEL
SMS, IVS4AS, G-A, +5
SMS, GLY56SER
SMS, VAL132GLY
SOX3, 33-BP DUP, NT711-743
SOX3, DUP
SOX3, 21-BP DUP
SRPX2, ASN327SER
SRPX2, TYR72SER
SYN1, TRP356TER
*SYN1, GLN555TER
*SYN1, ALA51GLY
*SYN1, ALA550THR
*SYN1, THR567ALA
SYP, 1-BP INS, 274A
SYP, 2-BP DEL/INS
SYP, 4-BP DEL, 829GACT
SYP, GLY217ARG
TIMM8A, 1-BP DEL, 151T
TIMM8A, 10-BP DEL, FS61TER
TIMM8A, GLU24TER
TIMM8A, CYS66TRP
TIMM8A, 1-BP DEL, 108G
TIMM8A, DEL
TIMM8A, ARG80TER
TIMM8A, IVS1, A-C, -23
TIMM8A, 1-BP DEL, 127T
TSPAN7, GLY218TER
TSPAN7, PRO172HIS
TSPAN7, 2-BP DEL, 564GT
UBE2A, GLN128TER
UBE2A, GLY23ARG
UBE2A, ARG11GLN
*UBE2A, PHE72SER
UPF3B, 4-BP DEL, 674GAAA
UPF3B, 2-BP DEL, 867AG
UPF3B, ARG430TER
UPF3B, TYR160ASP
ZDHC9, 4-BP DUP, 172CGCT
ZDHC9, 167+5G-C
ZDHC9, ARG148TRP
ZDHC9, PRO150SER
ZNF41, PRO111LEU
ZNF41, IVS2AS, A-C, -42
ZNF674, GLU118TER
*ZNF674, PRO412LEU
*ZNF674, MET343THR

ZNF711, 2-BP DEL, 2157TG
ZNF711, ARG525TER
ZNF81, SER179ASN

Table S3. List of All XLID Mutations and Variants Affecting the Same Amino Acid as a Reported XLID Mutation, which Are Listed in EVS

Chr position	Gene	mRNA Accession#	XLID-mutation = Variant found in EVS	AA Position/ Length total		Polyphen Prediction (OMIM vs EVS)	Grantham Score (OMIM/ EVS)	MAF (% EA/ AA/ All)	All Genotypes	Cons. (Phast Cons)	Cons. (GERP)	Ref & comments
a) XLID mutations present in EVS												
X:115303595	<i>AGTR2</i> ^a	NM_000686.4	c.62G>T p.Gly21Val (<i>rs121917810</i>)	21/364	benign	109	0.4608/ 0.0522/ 0.3124	TT=0/ TG=23/ T=10 / GG=4037/ G=2433	0.0	3.6		590 ID males were screened after the identification of <i>AGTR2</i> as an ID candidate due to its disruption in a translocation in an individual. p.G21V was present in the proband and his affected brother and in a third unrelated individual. ⁵⁴ 57 males with NS-ID were screened 1 was carrying p.G21V (but no segregation study was done) ⁵⁵ Reported in 4 individuals when screening 908 hemochromatosis individuals, suggesting it is a polymorphism. ⁵⁶
X:115304504	<i>AGTR2</i> ^a	NM_000686.4	c.971G>A p.Arg324Gln (<i>rs35474657</i>)	324/364	benign	43	0.0/ 0.7301/ 0.2651	AA=0/ AG=24/ A=4 / GG=4036/ G=2439	1.0	1.7		590 ID males were screened after the identification of <i>AGTR2</i> as an ID candidate due to its disruption in a translocation in a male. p.R324Q was detected in 3 unrelated cases and was not found in 510 control X-chromosomes. ⁵⁴
X:135861667	<i>ARHGEF6</i> ^a	NM_004840.2	c.166-11T>C p.? (<i>rs140322310</i>)	-	-	-	0.2378/ 0.0522/ 0.1704	GG=0/ GA=13/ G=5 / AA=4047/ A=2438	0.16	4.48		Screening of 119 additional individuals with NS-ID after its identification as an ID candidate led to the identification of this variation. It was reported in all affected males from the family and 5 carrier unaffected females. The predicted effect on splice efficiency is marginal (79% versus 77%), but results in exon 2 skipping. It is absent from 170 control X-chromosomes. ⁵⁷
X:41448815	<i>CASK</i>	NM_003688.3	c.1186C>T p.Pro396Ser (<i>rs137852820</i>)	396/922	benign	74	0.0/ 0.0782/ 0.0284	AA=0/ AG=3/ GG=4057/ G=2443	1.0	5.8		Reported in 3 individuals: 2 affected brothers and 1 affected female maternal cousin. It was not detected in 390 control X-chromosomes. The co-segregation study was not done in the healthy sister, who had 2 affected sons. Associated LOD score: 0.12. ²
X:31496431	<i>DMD</i>	NM_004006.2	c.8729A>T p.Glu2910Val (<i>rs41305353</i>)	2910/3686	benign	121	0.8472/ 6.8615/ 3.03	AA=7 / AT=249/ A=57 / TT=3803/ T=2386	1.0	5.4		One proband presenting with intermediate DMD phenotype was reported to carry two variations (p.E2910V, p.N2912D). The sister carried all 3 variants (p.E2910V, p.N2912D, p.H2921R). The mother carried only p.H2921R, and the father none. Germinal mosaicism? Already supposing that at least 1 variant is not fully pathogenic. ⁵⁸

X:31496426	DMD	NM_004006.2	c.8734A>G p.Asn2912Asp (rs1800278)	2912/3686	benign	23	0.8472/ 7.2006/ 3.1531	CC=9/ CT=255/ C=60/ TT=3795/ T=2383	1.0	1.7	One male presenting with intermediate DMD phenotype was reported to carry two variations (p.E2910V, p.N2912D). The sister carried all 3 variants (p.E2910V, p.N2912D, p.H2921R). The mother carried only p.H2921R, and the father none. Germinal mosaicism? Already supposing that at least 1 variant is not fully pathogenic. ⁵⁸
X:31496398	DMD	NM_004006.2	c.8762A>G p.His2921Arg (rs1800279)	2921/3686	benign	29	2.9727/ 0.4435/ 2.0547	CC=2/ CT=164/ C=49/ TT=3893/ T=2394	1.0	2.9	One male presenting with intermediate DMD phenotype was reported to carry two variations (p.E2910V, p.N2912D). The sister carried all 3 variants (p.E2910V, p.N2912D, p.H2921R). The mother carried only p.H2921R, and the father none. Germinal mosaicism? Already supposing that at least 1 variant is not fully pathogenic. ⁵⁸
X:54496615	FGD1	NM_004463.2	c.935C>T p.Pro312Leu (rs28935498)	312/962	unknown	98	0.1041/ 0.0/ 0.0663	AA=0/ AG=5/ A=2/ GG=4054/ G=2438	1.0	3.8	Three brothers carried the mutation, maternally transmitted. The mother was the only sample available for co-segregation testing. The observed phenotype was not suggestive of classical Aarskog syndrome. However, it was predicted to eliminate a β -turn, which may affect the orientations of an SH3 binding domain. ⁵⁹
X:153588207	FLNA	NM_001456.3	c.3872C>T p.Pro1291Leu (rs137853319)	1291/2640	benign	98	0.0153/ 0.0/ 0.0099	AA=0/ AG=0/ A=1/ GG=3859/ G=2375	0.9	5.3	The variant was transmitted by the affected mother and absent from 100 control X-chromosomes. It did not affect a very conserved residue, but the phenotype of the proband was somewhat similar to the one described by Hehr et al. ⁶⁰ (periventricular nodular heterotopia, craniofacial dysmorphic features and severe constipation). ⁶¹
X:70444261	GJB1	NM_000166.5	c.704T>G p.Phe235Cys (rs104894825)	235/284	benign	205	0.0/ 0.8344/ 0.3031	GG=0/ GT=28/ G=4/ TT=4030/ T=2439	0.854	4.9	This variant was identified in a girl with unusually more severe neuropathy matching rather Dejerine-Sottas disease than classical CMTX. It was inherited from her unaffected mother who showed unusual X-inactivation pattern. It was absent from 50 control chromosomes and detected in 6 additional CMTX samples (out of 12,720). The localization and trafficking of the mutant protein in cell culture was normal, but electrophysiological studies showed that the mutation caused abnormal hemichannel opening with excessive permeability of the plasma membrane and decreased cell survival. ⁶²
X:77086362	MAGT1 ^a	NM_032121.5	c.1028T>G p.Val343Gly/p.Val311Gly (rs145245774)	343/368	possibly-damaging	109	0.1785/ 0.0261/ 0.1231	CC=0/ CA=8/ C=5/ AA=4051/ A=2434	0.989	5.49	This missense variant was identified in one male and his affected brother and nephew, and not in the non-affected sister. The mutation was annotated p.G311V but corresponds in fact to the p.G343V described in EVS (see electropherogram profile in the paper). This variant was not found in 267 control X-chromosomes. ⁶³

X:119005968	<i>NDUFA1</i>	NM_004541.3	c.94G>C p.Gly32Arg (<i>rs1801316</i>)	32/71	Probably-damaging	125	0.9958/ 0.1043/ 0.6722	CC=0/ CG=53/ C=18 / GG=4007/ G=2425	0.8	3.8	It was identified in two independent families. Complex I was specifically reduced to 5% to 10% residual activity in both unrelated probands. It was inherited from both carrier mothers, and absent from 150 controls even though it was already reported in dbSNP. ⁶⁴
X:19375782	<i>PDHA1</i>	NM_000284.3	c.844A>C p.Met282Leu (<i>rs2229137</i>)	282/391	benign	15	0.0595/ 0.2086/ 0.1136	CC=0/ CA=8/ C=4 / AA=4052/ A=2439	1.0	5.5	This missense variant was found in 1 female (dysmorphism, microcephaly, hypotonia, brain atrophy) with PDH activity within normal range, and X inactivation (80:20). She was born from consanguineous parents. She presented with elevated lactate, but normal amount of immunoreactive protein. Her brother showed a more severe phenotype but DNA sample was unavailable because of his early death. ⁶⁵
X:23397873	<i>PTCHD1</i> ^a	NM_173495.2	c.517A>G p.Ile173Val (<i>rs147324438</i>)	173/889	benign	29	0.0595/ 0.0/ 0.0379	GG=0/ GA=2/ G=2 / AA=4058/ A=2441	1.0	5.06	This missense variant was reported in a male with autism, inherited from his unaffected mother. It was absent from 1'100 control individuals. The proband did not have siblings, which did not allow to support or exclude the pathogenicity of this variant. ⁴⁴
X:23353209	<i>PTCHD1</i> ^a	NM_173495.2	c.217C>T p.Leu73Phe	73/889	probably-damaging	22	0.0/ 0.0261/ 0.0095	TT=0/ TC=1/ CC=4059/ C=2443	1.0	4.46	This variant was reported in a male with autism, inherited from his unaffected mother. It was absent from 869 control individuals. This variant did not segregate with the ASD status in the family since it was present in a supposedly unaffected brother, and absent from an affected one, already suggesting it might not be the causative mutation. ⁴⁴
X:99922289	<i>SRPX2</i> ^a	NM_014467.2	c.980A>G p.Asn327Ser (<i>rs121918363</i>)	327/466	benign	46	0.1635/ 0.0/ 0.1041	GG=0/ GA=8/ G=3 / AA=4052/ A=2440	1.0	5.5	This variant was the first mutation identified in <i>SRPX2</i> and was absent from 554 control X-chromosomes. It co-segregated with the disease phenotype since it was present in all affected females and transmitted by the affected maternal grandfather. It was shown to affect the protein N-glycosylation. ⁶⁶
X:99917224	<i>SRPX2</i> ^a	NM_014467.2	c.215A>C p.Tyr72Ser (<i>rs121918364</i>)	72/466	benign	144	0.0149/ 0.0/ 0.0095	CC=0/ CA=0/ C=1 / AA=4060/ A=2442	1.0	5.1	This variant was the second mutation identified in <i>SRPX2</i> when screening 172 additional subjects. It was transmitted by the healthy mother, present in 2 affected aunts and also in an unaffected aunt. It was absent from 624 controls. ⁶⁶
X:47478976	<i>SYN1</i> ^a	NM_006950.3	c.152C>G p.Ala51Gly	51/706	possibly-damaging	60	0.0219/ 1.7629/ 0.6007	CC=0/ CG=30/ C=11 / GG=2659/ G=1436	0.718	3.08	This missense variant was detected in one epileptic female without cognitive impairment and in one ASD male also carrying the p.T567A variant, already suggesting one of the two variants might not contribute to the phenotype. ⁴⁸
X:38535032	<i>TSPAN7</i>	NM_004615.3	c.515C>A p.Pro172His (<i>rs104894951</i>)	172/250	benign	77	0.1338/ 0.0/ 0.0852	AA=0/ AC=8/ A=1 / CC=4051/ C=2442	0.6	3.6	This variant was identified in one XLID family and cosegregated with the disease in all but 1 affected individual. After neurological reassessment, linkage analysis excluded this gene. ⁶⁷ It was then confirmed that the linkage data did not match with a mutation in <i>TSPAN7</i> ⁶⁸ Additional screening of <i>TSPAN7</i> in 105 ID

											males revealed again the p.P172H variant. The mother and the sister were both unaffected carriers. ⁶⁹
X:47308837	<i>ZNF41</i> ^a	NM_007130.2	c.332C>T p.Pro111Leu (rs104894955)	111/780	benign	98	0.1486/ 0.0/ 0.0947	AA=0/ AG=8/ A=2 / GG=4051/ G=2441	1.0	3.1	The screening of <i>ZNF41</i> in 210 XLID cases revealed this missense variant in one proband. It was also present in one affected brother, transmitted by the mother. No additional samples were available to do a full co-segregation analysis. It was not found in 401 controls. ⁷⁰
X:47315839	<i>ZNF41</i> ^a	NM_153380.2	c.73-42 p.?	-	-	-	0.0297/ 0.3129/ 0.1325	GG=0/ GT=9/ G=5 / TT=4051	0.197	-1.56	The screening of <i>ZNF41</i> in 210 XLID cases revealed this variant in one proband. It was transmitted by the mother, and also present in a mildly affected sister. However, no difference of expression could be detected in the predominant <i>ZNF41.1</i> transcript, just an additional transcript was present. It was not found in 405 controls. ⁷⁰
X:117959226	<i>ZCCHC12</i> ^a	NM_173798.2	c.19C>T p.Arg7Cys (rs35356061)	4/403	benign	180	0.0149/ 0.8344/ 0.3124	TT=0/ TC=28/ T=5 / CC=4032/ C=2438	0.0080	2.17	This variant was identified during the screening of a cohort of 729 ID males and 494 controls. It was detected in 4/729 males with ID and 1/494 controls. In one family, this variant did not segregate with the disease status, and in the 3 other families no DNA sample was available from the parents. The observed residual function of the protein was showing 40% of activity. All those information already suggested it was a polymorphism. ⁶

b) XLID mutation and EVS variant affecting the same amino acid position

Chr position	Gene	mRNA Accession#	XLID-mutation	Variant found in EVS	AA Position/ Length total	Polyphen Prediction (OMIM vs EVS)	Grantham Score (OMIM/ EVS)	MAF (% EA/ AA/ All)	All Genotypes #	Cons. (Phast Cons)	Cons. (GERP)
X:153001649	<i>ABCD1</i>	NM_000033.3	c.1165C>G p.Arg389Gly (rs128624215)	c.1165C>T p.Arg389Cys	389/746	Probably-damaging/Probably-damaging	125/180	0.0/ 0.0261/ 0.0095	TT=0/ TC=1/ CC=4059/ C=2443	1.0	4.8

X:115303594	<i>AGTR2</i> ^a	NM_000686.4	c.62G>T p.Gly21Val (<i>rs121917810</i>)	c.61G>A p.Gly21Arg	21/364	benign/benign	109/125	0.0149/ 0.0/ 0.0095	AA=0/ AG=1/ GG=4059/ G=2443	0.0	1.8
X:32716111	<i>DMD</i>	NM_004006.2	c.835A>G p.Thr279Ala (<i>rs128627255</i>)	c.836C>T p.Thr279Met	279/3686	Probably- damaging/Probably- damaging	58/81	0.0149/ 0.0/ 0.0095	AA=0/ AG=1/ GG=4057/ G=2437	1.0	5.6
X:21863324	<i>MBTPS2</i>	NM_015884.3	c.261G>A p.Met87Ile (<i>rs122468177</i>)	c.260T>C p.Met87Thr	87/520	Probably- damaging/Probably- damaging	10/81	0.0149/ 0.0/ 0.0095	CC=0/ CT=0/ C=1/ TT=4060/ T=2442	1.0	5.81
X:38240681	<i>OTC</i>	NM_000531.5	c.386G>A p.Arg129His (<i>rs66656800</i>)	c.385C>T p.Arg129Cys (<i>rs140046498</i>)	129/355	Probably- damaging/Probably- damaging	29/180	0.0149/ 0.0261/ 0.0189	TT=0/ TC=2/ CC=4057/ C=2443	1.0	5.0
X:99922290	<i>SRPX2</i> ^a	NM_014467.2	c.980A>G p.Asn327Ser (<i>rs121918363</i>)	c.981C>G p.Asn327Lys	327/466	benign/benign	46/94	0.0/ 0.0261/ 0.0095	GG=0/ GC=1/ CC=4059/ C=2443	1.0	-0.2
X:133609228	<i>HPRT</i>	NM_000194.2	c.151C>G p.Arg51Gly (<i>rs137852494</i>)	c.152G>A p.Arg51Gln	51/219	benign/benign	125/43	0.0/ 0.0261/ 0.0095	AA=0/ AG=0/ A=1/ GG=4060/ G=2442	1.0	4.7
X:99662275	<i>PCDH19</i>	NM_001184880.1	c.1322T>A p.Val441Glu (<i>rs132630323</i>)	c.1321G>C p.Val441Leu (<i>rs200126728</i>)	441/1149	Probably- damaging/Probably- damaging	121/32	0.0604/ 0.0/ 0.0388	GG=0/ GC=4/ CC=3955/ C=2395	0.9	5.9
X:73740842	<i>SLC16A2</i>	NM_006517.3	c.671C>T p.Ala224Val (<i>rs104894936</i>)	c.670G>A p.Ala224Thr	224/614	unknown/unknown	64/58	0.0149/ 0.0/ 0.0095	AA=0/ AG=0/ A=1/ GG=4060/ G=2442	0.5	4.7

^a: Genes further discussed in the paper. In red: variations reported in hemizygous males or homozygous females from the NHLBI cohort.

Table S4. Reported Frameshift Variants in EVS in Our Set of 104 Selected Genes, Supposedly Implicated in XLID When Mutated

Chr position	Gene	mRNA Accession #	Resulting frameshift	variation/ Reference	MAF (% EA/ AA/ All)	All Genotypes	HW	Read depth	Cons. (GERP)	Location (exon affected/# total exons) & Comments
X:5811528	<i>NLGN4X</i>	NM_020742.2	p.Leu593Phefs*7	A/ACGAG	0.36/ 1.2998/ 0.6997	A1A1=20/ A1R=1/ A1=29/ RR=3900/ R=2134	No	169	4.1	exon 7/7
X:13764945	<i>OFD1</i>	NM_003611.2	p.Lys237Serfs*6	C/CA	1.5743/ 0.9401/ 1.3429	A1A1=12/ A1R=48/ A1=65/ RR=3888/ R=2241	No	47	4.2	exon 8/23. del of a A in a stretch of As
X:99662504	<i>PCDH19</i>	NM_001105243.1	p.Tyr366Leufs*10	CG/C	0.1092/ 0.3808/ 0.2082	A1A1=0/ A1R=10/ A1=11/ RR=3899/ R=2259	No	47	-0.2	exon 1/6 . Insertion of a C in a stretch of 6Cs
X:54069205	<i>PHF8</i> ^b	NM_001184896.1	p.Thr22Argfs*32	GTC/G	0.0/ 0.027/ 0.0098	A1A1=0/ A1R=0/ A1=1/ RR=3941/ R=2285	Yes	23	1.1	Alternative exon 2/22, in 5'UTR of other isoforms
X:48759667	<i>PQBPI</i> ^b	NM_001032381.1	p.Glu154Alafs*12	C/CAG	1.7441/ 1.6931/ 1.7255	A1A1=14/ A1R=58/ A1=90/ RR=3877/ R=2212	No	44	-6.6	Alternative exon 5A. Del AG in a stretch of 6 AGs.
X:47478983	<i>SYNI</i> ^a	NM_006950.3	p.Ala49Profs*95	CG/C	0.4852/ 0.7704/ 0.5799	A1A1=9/ A1R=14/ A1=2/ RR=2321/ R=1173	No	3	2.0	exon 1/13

X:47306866	ZNF41^a	NM_007130.2	p.Met768Cysfs*48	A/AT	0.0308/ 0.0269/ 0.0294	A1A1=0/ A1R=1/ A1=2 / RR=3949/ R=2305	Yes	122	0.8	exon 5/5
X:46360032	ZNF674^a	NM_001039891.2	p.Ile331*	A/ATG	0.3847/ 0.1554/ 0.3067	A1A1=13 / A1R=1/ A1=2 / RR=3602/ R=2223	No	85	-0.4	exon 6/6
X:79958985	BRWD3	NM_153252.4	p.Asp944Argfs*2	TC/T	0.2006/ 0.1074/ 0.1666	A1A1=0/ A1R=14/ A1=3 / RR=3936/ R=2302	Yes	45	3.8	exon24/41. Insertion of a G after 3 Gs.
X:71694561	HDAC8^b	NM_001166419.1	p.Pro252Glnfs*18	T/TG	0.0/ 0.141/ 0.0481	A1A1=0/ A1R=4/ RR=3114/ R=2081	Yes	87	2.8	Alternative exon8/8 (2/6 isoformes). Del of a G in a stretch of 4 Gs.
X:53310691	IQSEC2^{a, b}	NM_015075.1	p.Arg6Glyfs*24	C/CG	0.2056/ 0.259/ 0.2252	A1A1=0/ A1R=15/ A1=4 / RR=3404/ R=1596	Yes	7	-6.6	Alternative exon 1/1. Del of a G, in a stretch of 6 Gs.
X:53279788	IQSEC2^a	NM_001111125.2	p.Ala657Profs*35	G/GCT	0.4293/ 1.0725/ 0.661	A1A1=8 / A1R=38/ A1=11 / RR=3763/ R=2204	Yes	15	4.5	exon 5/14-15
X:153296066	MECP2	NM_001110792.1	p.Glu416Alafs*31 (rs61752992)	G/GCT	0.0155/ 0.0/ 0.0098	A1A1=0/ A1R=1/ RR=3943/ R=2272	Yes	53	5.6	exon4/4.

X:70360675	MED12	NM_005120.2	p.Ile2079Serfs*139	A/ATCCG	0.7466/ 1.4497/ 1.0049	A1A1=1/ A1R=79/ A1=19 / RR=3805/ R=2162	Yes	21	4.4	exon 42/45. Exon polyQ-rich
X:70360677	MED12	NM_005120.2	p.Arg2080Asnfs*140	CAA/C	0.3812/ 0.5747/ 0.4523	A1A1=1/ A1R=36/ A1=7 / RR=3850/ R=2169	Yes	21	3.4	exon 42/45. Exon polyQ-rich
X:17750060	NHS	NM_001136024.2	p.Ser1457Lysfs*12	A/AGC	0.0154/ 0.0/ 0.0098	A1A1=0/ A1R=1/ RR=3949/ R=2307	Yes	132	2.4	exon 10/10. del GC in a stretch of AGC repeats, poly-S rich.
X:17750063	NHS	NM_001136024.2	p.Ser1458Thrfs*13	A/AG	0.0154/ 0.0269/ 0.0196	A1A1=0/ A1R=1/ A1=1 / RR=3949/ R=2306	Yes	131	2.8	exon 10/10. del of a G in a stretch of AGC repeats, poly-S rich.
X:101096513	NXF5^a	NM_032946.2	p.Ser86Ilefs*9	A/AC	0.0154/ 0.0/ 0.0098	A1A1=0/ A1R=1/ RR=3949/ R=2307	Yes	147	-0.3	exon 6/16.
X:139586517	SOX3	NM_005634.2	p.Ala236Glyfs*141	C/CGG	0.1446/ 0.1269/ 0.1382	A1A1=1/ A1R=5/ A1=5 / RR=3501/ R=1664	Yes	5	1.4	exon 1/1. In a region of CGG repeats, poly-Alanine rich.
X:117959888	ZCCHC12^a	NM_173798.2	p.Lys228Asnfs*27	T/TA	0.0154/ 0.0/ 0.0098	A1A1=0/ A1R=1/ RR=3949/ R=2307	Yes	55	1.8	exon 4/4. del of A, in 3 As.

X:70472962	ZMYM3	NM_001171162.1	p.Pro48Leufs*65	A/AG	0.5971/ 0.7236/ 0.6428	A1A1=7/ A1R=25/ A1=25/ RR=3826/ R=2216	No	13	0.6	exon 3/26. Del of a C, in a stretch of 7 Cs.
X:47307488	ZNF41^a	NM_007130.2	p.Phe560Leufs*35	T/TG	0.0154/ 0.0/ 0.0098	A1A1=0/ A1R=1/ RR=3949/ R=2307	Yes	74	1.5	exon 5/5
X:84526124	ZNF711^a	NM_021998.4	p.Thr526Lysfs*23	A/ACCCATACTG GTGAG	0.0463/ 0.0269/ 0.0392	A1A1=0/ A1R=3/ A1=1/ RR=3947/ R=2306	Yes	45	5.2	exon 9/9

^a: genes further discussed in this paper. ^b: the resulting frameshift affects only some specific isoforms. In red: frameshifts reported in hemizygous males, or homozygous females. HW: allelic frequencies in agreement with Hardy-Weinberg equilibrium.

Table S5. Statistical Analyses on the 104 Genes: Number of Non-synonymous (N) and Synonymous (S) Variants Reported in EVS for Each Gene and Subsequent dN/dS Ratios, Computed as Detailed in Material & Methods

Gene	Transcript number	EVS		N & S sites in mRNA			dN/dS ratios		
		N	S	N sites	S sites	protein length	dN	dS	ratio
<i>ABCD1</i>	NM_000033.3	25	28	1647	588	745	0,015	0,048	0,319
<i>ACSL4/FACL4</i>	NM_022977	20	14	1642	491	711	0,012	0,028	0,428
<i>AFF2/FMR2</i>	NM_002025.3	57	34	3027	906	1311	0,019	0,038	0,502
<i>AGTR2</i> ^a	NM_000686.4	19	8	833	256	363	0,023	0,031	0,731 ^d
<i>APIS2</i>	NM_003916.3	2	4	367	104	157	0,005	0,038	0,142
<i>ARHGEF6</i> ^a	NM_004840.2	28	18	1801	528	776	0,016	0,034	0,456
<i>ARHGEF9</i>	NM_015185.2	12	13	1226	322	516	0,010	0,040	0,243
<i>ARX</i>	NM_139058.2	3	7	1236	451	562	0,002	0,016	0,156
<i>ATP6AP2</i> ^a	NM_005765.2	14	10	797	253	350	0,018	0,040	0,444
<i>ATP7A</i>	NM_000052.4	70	31	3424	1077	1500	0,020	0,029	0,710
<i>ATRX</i>	NM_000489.3	61	44	5915	1561	2492	0,010	0,028	0,366
<i>BCOR</i>	NM_001123385.1	93	63	3998	1267	1755	0,023	0,050	0,468
<i>BRWD3</i>	NM_153252.4	33	33	4169	1238	1802	0,008	0,027	0,297
<i>CASK</i>	NM_003688.3	17	24	2131	632	921	0,008	0,038	0,210
<i>CCDC22</i> ^b	NM_014008.3	40	17	1400	481	627	0,029	0,035	0,809 ^d
<i>CDKL5</i>	NM_003159.2	28	33	2375	715	1030	0,012	0,046	0,255
<i>CLIC2</i> ^b	NM_001289.4	6	5	575	166	247	0,010	0,030	0,346
<i>CNKSR2</i> ^b	NM_014927.3	22	19	2398	704	1034	0,009	0,027	0,340
<i>CUL4B</i>	NM_003588.3	13	12	2150	589	913	0,006	0,020	0,297
<i>DCX</i>	NM_000555, NM_178152	8	5	1019	304	441	0,008	0,016	0,478
<i>DKC1</i>	NM_001363.3	10	16	1184	358	514	0,008	0,045	0,189
<i>DLG3</i>	NM_021120.3	16	20	1863	588	817	0,009	0,034	0,253
<i>DMD</i>	NM_000109.3	224	114	8650	2382	3677	0,026	0,048	0,541
<i>FANCB</i>	NM_001018113.1	50	10	2013	564	859	0,025	0,018	1,400 ^d
<i>FGD1</i>	NM_004463.2	25	30	2167	716	961	0,012	0,042	0,276
<i>FLNA</i>	NM_001110556.1	97	125	5952	1989	2647	0,016	0,063	0,259
<i>FMR1</i>	NM_002024.5	16	14	1465	431	632	0,011	0,033	0,336
<i>FRMPD4</i> ^b	NM_014728.3	57	46	3030	936	1322	0,019	0,049	0,383
<i>FTSJ1</i>	NM_177439.1	15	16	738	244	327	0,020	0,066	0,310
<i>GDI1</i>	NM_001493.2	8	20	1027	314	447	0,008	0,064	0,122
<i>GK</i>	NM_001205019.1	9	12	1288	390	559	0,007	0,031	0,227
<i>GPC3</i>	NM_001164617.1	25	15	1403	406	603	0,018	0,037	0,483
<i>GRIA3</i>	NM_007325.4	19	17	2061	622	894	0,009	0,027	0,337
<i>HADH2</i>	NM_004493.2	4	4	578	206	261	0,007	0,019	0,356
<i>HCFC1</i> ^b	NM_005334.2	50	80	4477	1628	2035	0,011	0,049	0,227
<i>HCCS</i>	NM_005333.4	10	6	625	180	268	0,016	0,033	0,479
<i>HDAC8</i>	NM_018486.2	8	8	860	271	377	0,009	0,030	0,315
<i>HPRT1</i>	NM_000194.2	4	5	504	150	218	0,008	0,033	0,238
<i>HUWE1</i> ^c	NM_031407.4	67	105	9976	3147	4374	0,007	0,033	0,201

<i>IDS</i>	NM_000202.5	38	20	1248	402	550	0,030	0,050	0,612
<i>IGBP1</i> ^b	NM_001551.2	19	11	793	224	339	0,024	0,049	0,487
<i>IKBKKG</i>	NM_001099857.1	12	12	980	277	419	0,012	0,043	0,283
<i>ILIRAPL1</i>	NM_014271.3	14	22	1606	482	696	0,009	0,046	0,191
<i>IQSEC2</i>	NM_001111125.1	14	20	3334	1130	1488	0,004	0,018	0,237
<i>KDM5C</i>	NM_004187.3	35	42	3532	1148	1560	0,010	0,037	0,271
<i>SHROOM4</i> ^b	NM_020717.3	86	28	3448	1031	1493	0,025	0,027	0,918 ^d
<i>KIAA2022</i> ^b	NM_001008537.2	54	34	3559	989	1516	0,015	0,034	0,441
<i>KLF8</i> ^b	NM_007250.4	16	6	821	256	359	0,019	0,023	0,831 ^d
<i>LICAM</i>	NM_000425.3	53	48	2866	905	1257	0,018	0,053	0,348
<i>LAMP2</i>	NM_002294.2	25	12	933	297	410	0,027	0,040	0,663
<i>MAGT1/ IAP</i> ^a	NM_032121.5	15	10	846	255	367	0,018	0,039	0,453
<i>MAOA</i> ^b	NM_000240.3	14	12	1209	372	527	0,012	0,032	0,359
<i>MBTPS2</i>	NM_015884.3	21	13	1173	384	519	0,018	0,034	0,529
<i>MECP2</i>	NM_004992.3	37	45	1102	356	486	0,034	0,126	0,266
<i>MED12</i>	NM_005120.2	26	50	4982	1549	2177	0,005	0,032	0,162
<i>MID1</i>	NM_000381.3	25	20	1539	462	667	0,016	0,043	0,375
<i>NAA10</i> ^b	NM_003491.2	2	8	544	161	235	0,004	0,050	0,074
<i>NDP</i>	NM_000266.3	7	0	302	97	133	0,023	0,000	-
<i>NDUFA1</i>	NM_004541.3	4	3	161	49	70	0,025	0,062	0,402
<i>NHS</i>	NM_198270.2	73	37	3711	1179	1630	0,020	0,031	0,627
<i>NLGN3</i> ^b	NM_181303.1	17	27	1910	634	848	0,009	0,043	0,209
<i>NLGN4X</i>	NM_020742.2	20	40	1868	580	816	0,011	0,069	0,155
<i>NSDHL</i>	NM_015922.2	34	17	851	268	373	0,040	0,064	0,629
<i>NXF5</i> ^a	NM_032946.2	30	11	851	244	365	0,035	0,045	0,783 ^d
<i>OCRL</i>	NM_000276.3	27	15	2105	598	901	0,013	0,025	0,511
<i>OFD1</i>	NM_003611.2	49	22	2381	655	1012	0,021	0,034	0,613
<i>OPHN1</i>	NM_002547.2	34	18	1866	540	802	0,018	0,033	0,547
<i>OTC</i>	NM_000531.5	17	10	815	247	354	0,021	0,040	0,515
<i>PAK3</i>	NM_001128168.1	13	14	1342	398	580	0,010	0,035	0,275
<i>PCDH19</i>	NM_001105243.1	37	36	2492	812	1101	0,015	0,044	0,335
<i>PDHA1</i>	NM_000284.3	15	8	890	280	390	0,017	0,029	0,589
<i>PGK1</i>	NM_000291.3	24	5	959	293	417	0,025	0,017	1,465 ^d
<i>PHF6</i>	NM_001015877.1	6	4	859	236	365	0,007	0,017	0,411
<i>PHF8</i>	NM_001184896.1	17	26	2428	752	1060	0,007	0,035	0,203
<i>PLP1</i>	NM_001128834.1	2	6	620	211	277	0,003	0,028	0,113
<i>PORCN</i>	NM_203475.1	16	16	1029	355	461	0,016	0,045	0,345
<i>PQBPI</i>	NM_005710.2	2	8	606	189	265	0,003	0,042	0,078
<i>PRPS1</i>	NM_002764.3	0	7	734	220	318	0,000	0,032	0,000
<i>PTCHD1</i> ^c	NM_173495.2	29	25	2025	639	888	0,014	0,039	0,366
<i>RAB39B</i>	NM_171998.2	1	7	488	151	213	0,002	0,046	0,044
<i>RBM10</i>	NM_001204468.1	16	35	2263	722	995	0,007	0,048	0,146
<i>RPL10</i> ^b	NM_006013.3	2	4	491	151	214	0,004	0,027	0,154
<i>RPS6KA3</i>	NM_004586.2	10	14	1712	508	740	0,006	0,028	0,212
<i>SLC16A2</i>	NM_006517.3	20	9	1218	400	539	0,016	0,023	0,729 ^d

<i>SLC6A8</i>	M_005629.3	14	29	1426	479	635	0,010	0,061	0,162
<i>SLC9A6</i>	NM_001042537.1	11	16	1592	512	701	0,007	0,031	0,221
<i>SMC1A</i>	NM_006306.2	8	23	2911	788	1233	0,003	0,029	0,094
<i>SMS</i>	NM_004595.3	6	16	846	252	366	0,007	0,064	0,112
<i>SOX3</i>	NM_005634.2	6	8	977	361	446	0,006	0,022	0,277
<i>SRPX2</i> ^a	NM_014467.2	31	14	1050	345	465	0,030	0,041	0,728 ^d
<i>SYN1</i> ^c	NM_006950.3	12	12	1570	545	705	0,008	0,022	0,347
<i>SYP</i>	NM_003179.2	9	8	705	234	313	0,013	0,034	0,373
<i>TIMM8A</i>	NM_004085.3	3	4	230	62	97	0,013	0,065	0,201
<i>TSPAN7</i>	NM_004615.3	9	3	564	183	249	0,016	0,016	0,973 ^d
<i>UBE2A</i>	NM_003336.2	0	1	351	105	152	0,000	0,010	0,000
<i>UPF3B</i>	NM_080632.2	19	10	1153	297	483	0,016	0,034	0,489
<i>ZCCHC12/ SIZN1</i> ^a	NM_173798.2	19	14	928	278	402	0,020	0,050	0,406
<i>ZDHHC9</i>	NM_016032.3	2	12	832	260	364	0,002	0,046	0,052
<i>ZDHHC15</i> ^b	NM_144969.2	17	8	781	231	337	0,022	0,035	0,628
<i>ZNF261/ ZMYM3</i> ^b	NM_201599.2	31	42	3129	982	1370	0,010	0,043	0,232
<i>ZNF41</i> ^a	NM_007130.2	45	17	1850	487	779	0,024	0,035	0,696
<i>ZNF674</i> ^a	NM_001039891.2	28	10	1375	368	581	0,020	0,027	0,750 ^d
<i>ZNF711</i>	NM_021998.4	15	15	1795	489	761	0,008	0,031	0,272
<i>ZNF81</i> ^a	NM_007137.3	25	11	1572	411	661	0,016	0,027	0,595

^a, ^b, ^c: genes further discussed in this paper; ^a: Gene for which implication in ID is questioned regarding current evidences and EVS data; ^b: genes missing replication studies in order to be fully considered as implicated in ID; ^c: genes for which implication in ID is very likely, despite some contradictory observations in EVS. ^d: dS/dN ratios superior to the 90th percentile (0.723)

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